II. REMARKS

Formal Matters

Claims 1, 2, 6-18, 20-22, 25, and 26 are pending after entry of the amendments set forth herein.

Claims 1, 2, and 6-25 were examined and were rejected.

Claims 1, 6, 8-11, 14, 16, 17, 22, and 25 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as acquiescence to any objection or rejection of any claim. Support for the amendments to claims 1, 11, and 22 is found in the claims as originally filed, and throughout the specification, e.g., at paragraph 0044. No new matter is added by these amendments.

Claims 19, 23, and 24 are canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claims. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Claim 26 is added. Support for new claim 26 is found in the claims as originally filed (e.g., claim 5 as originally filed), and throughout the specification, including the following exemplary location: Substitute Specification, paragraph 0043. Accordingly, no new matter is added by new claim 26.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Examiner Interview

The undersigned Applicants' representative thanks Examiner Robert Hayes and Examiner Sharon Hurt for the courtesy of a telephonic interview which took place on November 16, 2009, and which was attended by Examiners Hayes and Hurt, and Applicants' representative Paula A. Borden.

During the interview, the rejections under 35 U.S.C. §112, second paragraph, 35 U.S.C. §112, first paragraph, and 35 U.S.C. §103(a) were discussed.

Withdrawn rejection

Applicants note with gratitude that the rejection of claims 1, 2, and 6-19 under 35 U.S.C. §103(a) over Yang in view of Kumar and Bujard, raised in the October 27, 2008 Office Action, has been withdrawn.

Claim objection

Claim 19 was objected to.

Claim 19 is cancelled without prejudice to renewal, thereby rendering this objection moot.

Rejection under 35 U.S.C. §112, second paragraph

Claims 1, 2, and 6-25 were rejected under 35 U.S.C. §112, second paragraph.

The Office Action stated that the "claims are drawn to a *Plasmodium falciparum* MSP-1 protein reduced in AT content compared to the wild type sequence." Office Action, page 3. Applicants respectfully traverse the rejection.

First, Applicants note that claim 5 as originally filed on April 19, 2005 depends from claim 1 and recites that the "nucleic acid coding for MSP-1 is reduced in its AT content compared to the wild type sequence." The June 23, 2006 Office Action included a rejection relating to this phrase; the January 9, 2007 Office Action indicated that the rejection was withdrawn.

Secondly, Applicants note that claim 1 recites that the nucleic acid is reduced in its AT content. Thus, the Office Action erred in stating that the claims are drawn to a *Plasmodium falciparum* MSP-1 protein reduced in its AT content. As such, claims 1, 2, and 6-25 are clear and need not be amended.

Conclusion as to the rejection under 35 U.S.C. §112, second paragraph

Applicants submit that the rejection of claims 1, 2, and 6-25 under 35 U.S.C. §112, second paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejections under 35 U.S.C. §112, first paragraph

Claims 20 and 22-25 were rejected under 35 U.S.C. §112, first paragraph, as allegedly reciting new matter. Claims 13-25 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Claims 13-25 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement.

Claims 20 and 22-25; new matter

The Office Action stated that Applicants added new matter in the claims added on June 27, 2008 and April 23, 2009 by adding "wherein the vaccine does not comprise an adjuvant." Applicants respectfully traverse the rejection.

First, Applicants note that this rejection could have been raised earlier. As the Office Action acknowledged, the phrase "wherein the vaccine does not comprise an adjuvant" appears in a claim filed along with the June 27, 2008 response. As noted in the MPEP §707.07(g), piecemeal examination should be avoided as

much as possible, and the examiner ordinarily should reject each claim on all valid grounds available.

Secondly, it is noted that in the protocol and results described in paragraphs 0084-0098, no adjuvant was used. Thus, these paragraphs provide adequate support for the phrase "wherein the vaccine does not comprise an adjuvant." It is noted that the paragraphs describing the experiments and results relating to Figures 3A and 3B note that in some instances, an adjuvant was used. Thus, where no adjuvant is mentioned, no adjuvant was used. It is standard, where a vaccination protocol is described, to indicate when an adjuvant is used. It is not standard to indicate what is missing from a solution.

As indicated in paragraphs 0084-0098, no adjuvant was used. As such, the instant specification provides support for the phrase "wherein the vaccine does not comprise an adjuvant."

Claims 13-25; written description

The Office Action appeared to focus the rejection on the recitation of "mutein."

Claim 1 and 22 are amended to delete recitation of "mutein"; and claim 24 is cancelled without prejudice to renewal. Claim 13 refers to the recombinant virus of claim 1. As such, the amendment of claim 1 and 22 to delete recitation of "mutein" applies to claim 13.

As discussed during the telephone interview, MVA was well known in the art. See, e.g., specification, paragraph 0040, citing a 1974 publication. Furthermore, as discussed during the telephone interview, merozoite surface protein-1 (MSP1) amino acid sequences and fragments were well known in the art. See, e.g., specification, paragraph 0042 and paragraph 75 (citing a 1987 publication). See also, e.g., Stafford et al. (1994) *Mol. Biochem. Parasitol.* 66:157.

Claims 13-25; enablement

The Office Action appeared to focus the rejection on the recitation of "mutein."

Claim 1 and 22 are amended to delete recitation of "mutein"; and claim 24 is cancelled without prejudice to renewal. Claim 13 refers to the recombinant virus of claim 1. As such, the amendment of claim 1 and 22 to delete recitation of "mutein" applies to claim 13.

Conclusion as to the rejections under 35 U.S.C. §112, first paragraph

Applicants submit that the above-discussed rejections under 35 U.S.C. §112, first paragraph, have been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejections.

Rejections under 35 U.S.C. §103(a)

Claims 1, 2, and 6-21 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Schneider et al. ((1998) *Nat. Med.* 4:397; "Schneider") in view of Yang et al. ((1997) *Vaccine* 15:1303-1313; "Yang"), Kumar et al (April, 2002) *Immunology Letters* 81:13-24), and Bujard et al. (WO 98/14583; "Bujard"). Claims 22-25 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Schneider in view of Yang, Kumar, and Bujard, and further in view of Sedegah et al. ((1994) *Proc. Natl. Acad. Sci. USA* 91:9866; "Sedegah").

Claims 1, 2, and 6-21 over Schneider in view of Yang, Kumar, and Bujard

The Office Action stated:

1) Schneider teaches a DNA plasmid vaccine with a recombinant modified vaccinia virus Ankara (MVA) expressing a *Plasmodium* antigen provided protection in mice against challenge;
2) Schneider does not teach using the MSP-1 protein, the *Plasmodium* strain 3D7, or an MSP-1 with reduced AT content;
3) Yang teaches a recombinant vaccinia virus encoding a *P. falciparum* merozoite surface antigen;
4) Kumar teaches a DNA plasmid vaccine encoding the merozoite surface protein 1 (MSP-1) from the 3D7 strain of *P. falciparum*, and teaches construction of a vaccinia recombinant expressing MSP-1; and
5) Bujard teaches a *Plasmodium* species that is stabilized by a process characterized by a reduction of the AT content.

The Office Action concluded that it would have been obvious to use a surface protein such as MSP-1 in a DNA plasmid vaccine as taught by Schneider from a strain as taught by Kumar. The Office Action asserted that it would have been obvious to increase stability of the vaccine preparation as taught by Schneider by "modifying the protein by reducing the AT content as taught by Bujard." Office Action, page 12. Applicants respectfully traverse the rejection.

The cited art does not disclose or suggest all of the claim limitations.

As described below, the cited art, taken together, does not disclose or suggest all of the claim limitations of claim 1. For example, the cited art does not disclose or suggest a recombinant MVA virus comprising at least one nucleic acid coding for: i) *Plasmodium falciparum* MSP-1 p42; ii) *Plasmodium falciparum* MSP-1 p42 and -38; or iii) *Plasmodium falciparum* MSP-1 p83, p30, p42, and p38.

Schneider

Schneider discusses use of plasmid DNA encoding *Plasmodium berghei* pre-erythrocytic antigens (thromobspondin-related adhesive protein (PbTRAP) and the circumsporozoite protein (PbCSP)) to immunize mice against challenge.

Schneider does not include any teaching or suggestion relating to ***Plasmodium falciparum***.

Schneider does not include any teaching or suggestion relating to **MSP-1**.

Schneider does not include any teaching or suggestion relating to **specific fragments or combinations of fragments of MSP-1**.

Schneider neither discloses nor suggests:

- a recombinant MVA virus comprising at least one nucleic acid coding for a ***Plasmodium falciparum*** antigen;
- a recombinant MVA virus comprising at least one nucleic acid coding for a *P. falciparum* **merozoite surface protein-1** antigen;
- a recombinant MVA virus comprising at least one nucleic acid coding for **at least one fragment** of *P. falciparum* MSP-1, where the at least one fragment is selected from: **i) p42; ii) p42 and p38; and iii) p83, p30, p42, and p38**.

Schneider discusses Plasmodium species that are not relevant to human malaria.

As discussed in the instant specification, there are four malaria species that infect humans: *Plasmodium malariae*, *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium falciparum*, with *Plasmodium falciparum* being responsible for almost all fatal infections. Specification, paragraph 0004.

Schneider relates to immunization of mice with antigens (other than MSP-1) from *Plasmodium berghei*. *Plasmodium berghei* does not infect humans; instead, *Plasmodium berghei* is used to generate models of rodent malaria. Schneider, page 397, column 1, second paragraph. **Schneider is thus not relevant to a recombinant virus comprising a nucleic acid encoding *Plasmodium falciparum* antigens.**

Schneider discusses Plasmodium antigens that are not merozoite surface proteins.

When an individual is bitten by a mosquito that carries malaria, sporozoites present in the material injected into the individual by the mosquito enter the bloodstream of the individual and migrate to the liver. Sporozoites infect liver cells, where they multiply into merozoites, rupture the liver cells, and escape back into the bloodstream. Merozoites in the bloodstream infect red blood cells, where they develop into ring forms, then

trophozoites (a feeding stage), then schizonts (a reproduction stage), then back into merozoites.

Schneider discusses use of plasmid DNA or MVA vectors encoding *Plasmodium berghei* pre-erythrocytic antigens (thromobspondin-related adhesive protein (**PbTRAP**) and the circumsporozoite protein (**PbCSP**)) to immunize mice against challenge. Both the TRAP and the circumsporozoite proteins are **sporozoite** stage proteins.

The MSP-1 complex of *P. falciparum* constitutes a major component at the surface of the erythrocyte-invading (**merozoite**) form of the parasite.

Thus, Schneider relates to proteins from a different stage of the *Plasmodium* life cycle than MSP-1.

Schneider indicates that use of MVA is not always successful in inducing protective immunity.

Schneider states that various prime-boost immunization strategies, with combination of various recombinant vaccinia virus strains and plasmid DNA, were tested for immunogenicity and protective efficacy. Schneider, page 397, column 2, first full paragraph. Schneider states that using plasmid DNA priming an recombinant MVA boosting, complete protection against sporozoite challenge was observed in two different mouse strains. Schneider states that "[t]his specific order of immunization **was essential for protection**." Schneider, page 397, column 2, first full paragraph, emphasis added. As shown in Table 1a of Schneider, use of MVA encoding PbCSP and PbTRAP for the first (priming) and second (boosting) immunizations resulted in very low protection; and use of MVA encoding PbCSP and PbTRAP for the first immunization, followed by use of plasmid DNA encoding PbCSP and PbTRAP for the second immunization, resulted in **no** protection.

Schneider noted that studies carried out in chimpanzee also involved priming with DNA (i.e., plasmid DNA encoding PbCSP and PbTRAP), followed by boosting with MVA (i.e., MVA encoding PbCSP and PbTRAP).

Thus, not only does Schneider not disclose or suggest all of the features of claim 1, Schneider in fact teaches away from use of MVA as a suitable vector for *P. falciparum* antigens.

Yang

Yang discusses use of a recombinant vaccinia virus encoding a 190 kDa merozoite surface antigen, with or without anchor and signal sequences. Yang **does not disclose or suggest any recombinant virus encoding *fragments* of MSP-1**.

Yang neither discloses nor suggests:

- a recombinant **MVA virus** comprising at least one nucleic acid coding for a *Plasmodium falciparum* antigen;
- a recombinant MVA virus comprising at least one nucleic acid coding for **at least one fragment** of *P. falciparum* MSP-1, where the at least one fragment is selected from: **i) p42; ii) p42 and p38; and iii) p83, p30, p42, and p38**.

The Office Action stated that the merozoite antigen is processed into fragments (30, 38, and 42 kDa), and stated that each gene was inserted into the thymidine kinase region of the vaccinia virus. Office Action, bridging sentence, pages 10 and 11. The Office Action appeared to imply that genes encoding the 30, 38, and 42 kDa fragments were inserted into the vaccinia virus. **They were not**.

Yang discusses a recombinant vaccinia virus encoding a C-terminal fragment (**amino acids 1047-1640**) region of MSP-1. Yang, page 1304, column 1, last 8 lines of first full paragraph.

> erythrocytes[29]. An anti-idiotype antibody derived from 2B10 recognized the C-terminal (1047–1640aa) region of MSA1 in a Western blot[29] and appears to recognize the same site on glycophorin A as the merozoite. Here we describe the effect of signal and anchor sequences on the biochemical processing and antibody response to this C-terminal region of MSA1 when expressed by a rVV.

Yang states that the C-terminal fragment is encoded by nucleotides 3553-5290 of the sequence set forth in GenBank Accession No. X02919. Yang, Table 1 and legend. As shown in Exhibit 1, nucleotides 3553-5290 of the X02919 sequence encode amino acids 1047-1621 of MSP-1. As shown in Figure 1 of the instant application, and as depicted schematically in Figure 6A of Kauth et al. (2003) *J. Biol. Chem.* 278:22257, amino acids 1047-1621 of MSP-1 **does not correspond to any of the MSP-1 fragments recited in claim 1**. Instead, as shown in Exhibit 2, amino acids 1047-1621 of MSP-1 begins within p38 and includes most of the amino acid sequence of p42. Thus, Yang discusses a fragment that is not p42, p38, p30, or p83.

Yang does not disclose or suggest a recombinant MVA virus comprising a nucleic acid encoding the particular recited fragments of *P. falciparum*.

Yang mentions in passing that MVA has been developed as an expression vector and shown to be equivalent to replication competent vaccinia virus in several vaccine models.

However, one cannot necessarily extrapolate from vaccinia virus to MVA. First, as noted previously, MVA is highly attenuated, compared to vaccinia virus. It was not necessarily predictable, based on the results of Yang with vaccinia virus, that recombinant MVA comprising a nucleic acid encoding fragments of *Plasmodium falciparum* MSP-1 would be efficacious.

Indeed, Schneider indicated that recombinant MVA encoding *P. berghei* pre-erythrocytic antigens, when administered to mice, in some instances provided no protection at all against challenge.

Kumar

Kumar discusses preparation of a DNA plasmid encoding the C-terminal 42-kDa region of merozoite surface protein 1 ($pMSP1_{42}$), and preparation of a recombinant vaccinia virus vector encoding the same C-terminal 42-kDa region.

The data contained in Kumar relate to the effect of **immunization with a DNA plasmid encoding MSP-1 p42** ($pMSP1_{42}$). Kumar, bridging sentence, pages 14-15; and page 15, column 1, section 2.1.1. under "Materials and Methods." In connection with the recombinant vaccinia virus (which was not MVA) construct encoding the same C-terminal 42-kDa region, Kumar states that this recombinant vaccina virus was used **to infect target cells for CTL analysis**. Kumar, page 15, column 2, section 2.2 under "Materials and Methods."

Kumar neither discloses nor suggests:

- a **recombinant MVA virus** comprising at least one nucleic acid coding for a *Plasmodium falciparum* antigen;
- a recombinant MVA virus comprising at least one nucleic acid coding for **at least one fragment** of *P. falciparum* MSP-1, where the at least one fragment is selected from: i) p42; **ii) p42 and p38; and iii) p83, p30, p42, and p38**.

Bujard

Bujard is entitled "Method for producing recombinants intended for use in a complete malaria antigen GP190/MSP1." Bujard discusses a nucleic acid encoding the complete malaria antigen, where the nucleic acid has a reduced AT content relative to wild-type sequence.

Bujard neither discloses nor suggests:

- a **recombinant MVA virus** comprising at least one nucleic acid coding for a *Plasmodium falciparum* antigen;
- a recombinant MVA virus comprising at least one nucleic acid coding for **at least one fragment**

of *P. falciparum* MSP-1, where the at least one fragment is selected from: **i) p42; ii) p42 and p38; and iii) p83, p30, p42, and p38**.

The Office Action has not established a prima facie case of obviousness.

As noted above, the cited art does not disclose or suggest all of the claim elements as recited in claim 1. Furthermore, in contrast to the Office Actions' assertions, the cited art does not provide motivation to make the modification suggested in the Office Action, because the references do not "teach a successful vaccine" where the vaccine would comprise a recombinant MVA comprising a nucleic acid encoding at least one fragment of *P. falciparum*.

As noted above, Schneider teaches that a recombinant MVA encoding *P. berghei* pre-erythrocytic antigens (thromobspondin-related adhesive protein and the circumsporozoite protein) in some instances **failed to induce protective immunity in mice**. As such, one skilled in the art, given Schneider, would **not** have had a reasonable expectation of success, as asserted in the Office Action. Therefore, recombinant MVA vector as claimed, or a vaccine composition comprising same, is **not** simply a predictable combination of prior art elements.

Furthermore, none of the cited art teaches or suggests a recombinant MVA virus comprising a nucleic acid encoding the MSP-1 fragments recited in claim 1. Schneider does not even discuss MSP-1 or any other merozoite antigens, but instead discusses sporozoite antigens. Yang does not discuss any of the recited fragments. Instead, Yang discusses a C-terminal MSP-1 fragment that is different from any of the recited fragments. Kumar discusses use of a recombinant vaccina virus (not a recombinant MVA virus) encoding MSP-1 p42, to infect target cells for CTL analysis. For immunization, Kumar used a plasmid vector encoding MSP-1 p42. Bujard discusses a recombinant vector encoding full-length (p190) MSP-1. Thus, the cited art does not disclose the combination of elements recited in claim 1.

The cited art does not disclose or suggest all of the claim elements of claim 1. Furthermore, Schneider teaches away from the proposed combination. Thus, the recombinant MVA vector as claimed, or a vaccine composition comprising same, is **not** simply a predictable combination of prior art elements. As such, Schneider, alone or in combination with Yang, Kumar, and Bujard, cannot render any of claims 1, 2, and 6-21 obvious.

Comments regarding the Office Action

The Office Action referred to Applicants arguments (see header at bottom of page 12, and first paragraph at top of page 13). However, as the rejection over the combination of Schneider, Yang, Kumar, and Bujard is being raised for the first time in the current Office Action, Applicants could not have previously presented any

arguments in response to the rejection.

Claims 22-25 over Schneider in view of Yang, Kumar, Bujard, and Sedegah

The Office Action stated that none of Schneider, Yang, Kumar and Bujard explicitly teaches a vaccine that does not comprise an adjuvant. The Office Action stated that Sedegah teaches an adjuvant-free malaria vaccine. The Office Action stated that it would have been obvious to make a malaria vaccine that does not comprise an adjuvant. Applicants respectfully traverse the rejection.

Claim 22 is amended to include language similar to that of claim 1. Furthermore, claim 22 as amended does not recite "wherein the vaccine does not comprise an adjuvant." As noted above, Schneider, Yang, Kumar, and Bujard do not disclose or suggest all of the claim elements of claim 1. The recombinant MVA vector as claimed, or a vaccine composition comprising same, is **not** simply a predictable combination of prior art elements.

Sedegah does not cure the deficiency of Schneider, Yang, Kumar, and Bujard. Sedegah relates to use of a plasmid DNA encoding *Plasmodium yoelii* circumsporozoite antigen. Sedegah neither discloses nor suggests a vaccine composition as recited in claim 22. Schneider, alone or in combination with Yang, Kumar, Bujard, and Sedegah, neither discloses nor suggests a composition as recited in claim 22. Furthermore, as noted above, Schneider does not provide a predictable success. As such, Schneider, alone or in combination with Yang, Kumar, Bujard, and Sedegah, cannot render claims 22 and 25 obvious.

Conclusion as to the rejections under 35 U.S.C. §103(a)

Applicants submit that the above-discussed rejections under 35 U.S.C. §103(a) have been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejections.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number GRUE-004.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: November 23, 2009

By: /Paula A. Borden, Reg. No. 42,344/
Paula A. Borden
Registration No. 42,344

BOZICEVIC, FIELD & FRANCIS LLP
1900 University Avenue, Suite 200
East Palo Alto, CA 94303
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

F:\DOCUMENT\GRUE (Gruenecker, Kinkeldey...)\004\GRUE-004_Response_OA_dated_7-21-09.doc